Case 4 Common Variable Immunodefficiency (Autosomal…) 25 year old

* Phenotype caused by many different genetic complications and is characterized by normal levels of B and T cells while low levels antibodies (specifically A,G,E, but high levels of anti-thyroid antibodies (unknown cause). Also a diagnostic lack of plasma cells
* Most commonly TACI gene deficiency (involved in somatic hypermutation)
* Often with gastric/resp diseases. Increased risk for lymphoma, gastric carcinoma and increased autoimmune diseases
* Treat with IVIgG
* Special BAFF, APRIL, TACI

Case 8 MHCII deficiency (chromosome6 and auto recessive)

* Low CD4 cells with normal amount of t cells, low numbers of Ig, subject to opportunistic and pyogenic and viral. Low B cells
* Like SCID impaired Tcells but still Tcells that respond to non specific T Cell mitogens

Case 9 DiGeorge

* No tbx1 which is needed for pharyngeal arches/pouches 3 and 4
* Cardiac, thyroid, calcium, facial, immunity problems

Case 24 IFN Gamma receptor

* JAK STAT isn’t producing the appropriate attack enzymes Bacteria survive in the lymphnodes
* TYPICALLY mycobacteria do not cause disease but in this case they do since you have impaired macrophage function

Case26

Case 51 Atopic Dermatitis

* Mediated by antigen specific TH2 cells
* Sensitization through langerhan cells and the deposition of the TH2 cells in the skin
* Dry itchy skin is the result of a lack of profilagrin (broken to filagrin which is hydrophilic) due to a genetic mutation. SCCE and SPINK5 also associated with the disease

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Case 1 x linked agammaglobulinemia

* No tonsils, BTK, no B cells (impaired Bcell maturation)
* BTK from proB -> Immature B

Case2 x linked CD40 Ligand Defficiency

* Pyogenic and Opportunistic infections, normal size lymphodes (CD40 is auto recessive)

Case 3 AID Defficiency (UNG is a look alike) (Chromosome 12 Autosomal Recessive) AID enzyme

* **SX Pyogenic (CD16, NK, IgG) but not subject to opportunistic infections, swollen lymph nodes (auto recessive)**
* Looks like xlinked agammaglobulinemia
* AID Mech Biochemical events underlying class switching have only been clarified relatively recently. Require AID which converts Cytidine to uridine. Uridine is known to trigger a DNA breakage and repair mechanism that underlies the class switch recombination. This mechanism uses UNG which removes the Uracil base creating a break in the DNA strand that will be repaired and make a new class. IF either are broken, the cell cannt class switch and only IgM is produced. AID is required for hypermutation. Point mutations are introduced at a high rate into the DNA that codes for the V region of both heavy and light chains. A process of selection then occurs. (Affinity maturation). Due to a short arm of chromosome 12 containing the AID gene. AID defects only impair the Bcell function and have no impact on the Tcell function since CD40 and CD40L are still intact for the Th2/Macrophage interaction. The biggest thing that is readily apparent on physical exam are swollen lymph nodes in AID/UNG deficient patients. Because these two enzymes are not necessary for the formation of germinal centers, these patients have large germinal centers responding to the Tcell stimulation but just not able to produce the appropriate class switch and hypermutation.

Case 7 Omenn Syndrome (B- T- NK+) (Auto Recessive) Rag 1 and 2 missense mutation

* Partial activation of Rag 1 and 2 (SCID is complete lack of Rag and NO B or T). Form oligo clonal Tcells. Proliferating from a smaller subset of Tcells. Travel to any organ and cause damage. The few T cells in the thymus go through expansion to excrete a lot of cytokines and Th2 cells (IL4,5) secretion of IL4 is an isotype switch to IgE and 5 recruits eosinophils. NOTE Rag is used in both B cell and Tcell development
* **SX Enlarged organs oligoclonal T cells, High IgE, No AIRE (used to regulate over reactive T cells b/c involved in negative selection), rash (chemokine), diarrhea (protracted…. The natural flora), persistent bacterial infections, splenomegaly, swollen lymph nodes. Need a bone marrow transplant but usually lethal**

Case 15 Chediak Higashi Syndrome (Auto recessive CHS1) Vesicular trafficiking with CAH1

* Vesicular trafficking in the cells is impaired, impaired innate immunity (no lysosomal trafficking). TCL, NK not proper cytotoxicity. Subject to bacterial infections but not necessarily viruses
* **SX: fair skin, ear/pneumonia, small/thin, hepatosplenomegally needing a bone marrow transplant but ultimately leads to neuro (problems with exocytosis in axons). Usually trouble with clotting because no vesicular trafficking.**
* NBT test shows that the neutrophils were fine but leukocytes **giant cytoplasmic granules. NBT based on NADPH oxidase function.**
* CHS1 not sure exactly how it has a role in trafficking cells.
* High lymphocytes in the accelerated phase because the bacterial antigens continue to present but do not respond. (this is later in the pathogenesis)

Case 16 Wiskott-Aldrich Syndrome (xlinked) Actin rearrangement due to WASP

* Actin cytoskeleton is not working appropriately. The impaired cytoskeleton rearrangement in Tcell activation. Also cannot interact appropriately with B cells. Poor clotting in due to Megakaryocyte impairment.
* **SX: Pyogenic and Opportunistic infections TCL, NK and Antibody issues. Eczema, staph, pneumonia, asthma, bloody diarrhea, positive coulbms test (autoimmune hemolytic anemia). Icreased IgA and E (low M) with normal B and T cells, low CD3 function so normal amounts of Tcell but not functional. Low WAS protein (C-T change missense)**
* No WASP… splenic architecture impaired and no carbohydrate specific antibodies (so low IgM)
* IVIG, bone marrow transplant, chemo
* NOTE: WASP is expressed in Leukocytes and Megakaryocytes

Case 50 Allergenic Asthma (Atopic…. Not autosomal or xlinked) Overactivation of TH2 to cause IgE to stimulate Mast cells

* Histamine degranulation
* Allergic Asthma is regulated by IgE (IL4) and Eosinophils (IL5)(Type I). Once an individual has been sensitized, the rection becomes worse with each exposure. CD4 cells present to Bcells to make antibodies which attatch to mast cells. Once the antigen is encountered again, the mast cell degranulates. Histamine increases vascular permeability and causes smooth muscle contraction. Late phase of the Rx, the arachidonic acid is broken down to prostaglandins and leukotrienes which increase blood flow and extravasation. IL3,4,5 and TNF alpha all prolong the reaction and cause an influx of monocytes, tcells and eosinophils. In asthma, the inflammatory response increases hypersensitivity of the airways causing them to react to exercise, pollutants and cold air

Case 12 MHC I deficiency (Recessive)

* Different genotypes (TAPS, MHC, Proteases)
* Low CD8, problems with viral infection (influenza, vasculitis, granulomatous)
* Some viruses can stimulate MHCI and note that gamma/delta chains develop independent of MHC control of the thymus
* Elevated IgG
* Chromosome 6 for TAP 1

Case 25 SCN (mixed)

* Young child with extacellular bacterial infections and invasive fungal infection
* Normal blood tests except super low neutrophils (below 500)
* Bone marrow test to see where the problem is
* ELA gene is a target to monitor

Case 32 Factor I insufficiency (recessive chromosome 4 and only the full homo have the symptoms)

* Subject to pyogenic and agglutination of RBC with C3b antibody
* iC3b is bound to TCR 3 and 4 to activate phagocytosis of macrophages
* Nieserria infections and increased pyogenic
* Hypersensitivity due to C3a (his natural level of C3a is higher than most of us)
* C3b binds to CR1
* High rate of C3 consumption and thus factor B

Case 35 Systemic onset Juvenile Idiopathic Arthritis

* sJIA is an auto-inflammatory immune condition consisting of arthritis along with high spiking fevers, fatigue, rash and enlargement of lymph nodes and spleen
* clinically diagnosed (idiopathic)
* Initial treatment includes nonsteroidal anti-inflammatory medications along with corticosteroids
* Newer therapies relying on the inhibition of IL-1, and body tempand IL-6 have showed promising results
* Arthritis, daily fever for 2 weeks, rash, lymph nodes, serositis
* IL1- APC cells to fibroblasts and endothelial cells. Increase adhesion, body temp and regulate blood cell devel
* IL6- to causing inflammation, stimulates osteoclasts, can also act as an inflammatory regulator, prolif of immune cells
* TNF- regulate production and apoptosis released mostly by macrophages

Case 17 APECED

* Self reactive t cells since the patient is deficient in AIRE
* Susceptible to *C.albicans.*
* Thyroid/endocrine glands are being targeted
* Exodermal elements are altered because of autoimmune attack

Case 27 LAD

* No CD18

Case 52

* Small immune complexes from over large doses of antigen (direct antigen or hapten)
* Large complexes are taken up by classical complement
* Type III hypersensitivity due to small immune complexes deposit on local tissues
* classic complement with C3a and C5a to attact neurtrophils and increased inflammation
* platelet aggregation with hemorrhage.